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Review:

Regulation of bile acid metabolism-related signaling pathways by gut microbiota in diseases*

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Abstract: Over the past decade, there has been increasing attention on the interaction between microbiota and bile acid metabolism. Bile acids are not only involved in the metabolism of nutrients, but are also important in signal transduction for the regulation of host physiological activities. Microbial-regulated bile acid metabolism has been proven to affect many diseases, but there have not been many studies of disease regulation by microbial receptor signaling pathways. This review considers findings of recent research on the core roles of farnesoid X receptor (FXR), G protein-coupled bile acid receptor (TGR5), and vitamin D receptor (VDR) signaling pathways in microbial–host interactions in health and disease. Studying the relationship between these pathways can help us understand the pathogenesis of human diseases, and lead to new solutions for their treatments.

Key words: Gut microbiota; Bile acid; Farnesoid X receptor; Vitamin D receptor; Metabolism
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1 Introduction

There are many kinds of microorganisms in the human gastrointestinal tract, but because of the difficulty of cultivating many of them, it has not been possible to provide complete information on gut microbiota. However, with developments in science and technology, advances in sequencing technology and bioinformatics have revealed the complexity of the human microbiome and have identified *Bacteroides*, *Firmicute*, and *Lactobacilli* as the most prevalent components of the gut microbiota.

Interaction between gut microbiota and the host results in the formation of multiple metabolites, such as secondary bile acids (BAs) and choline, which can affect gut health (Sung et al., 2017). Therefore, the microbial community is related to the nutrition, metabolism, and immunity of the host. Most of these functions are interconnected and tightly intertwined with human physiology. Loss of an appropriate balance between different gut microflora can produce different metabolites with different inflammatory properties, which can cause disease. Gut microflora can promote endothelial cell proliferation, stimulate intestinal cell differentiation, and prevent *Clostridium difficile* colonization by regulating BA metabolism (Tremaroli and Bäckhed, 2012; Thaiss et al., 2016).

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Therefore, the interaction between gut microbiota, the immune system, and the intestinal barrier can inhibit the growth of pathogenic bacteria (Giorgetti et al., 2015). Many studies have shown that gut microbiota also play an important role in related diseases (Neish, 2009). In the adult gut, imbalance of the gut microbiome can lead to metabolic, digestive, and cardiovascular diseases, and even cancer. It is for this reason that there has been increasing research attention on intestinal microflora.

At present, short-chain fatty acid (SCFA) metabolites are the most widely studied metabolites in host–microbiota interactions. SCFAs are synthesized by colonic bacteria through fermentation of ingested fibers. They can modulate cytokine production and the expansion of regulatory T cells (Lee and Hase, 2014), and augment immunity via immunoglobulin A (IgA) production by plasma cells (Pabst, 2012). T cell differentiation may affect the gut microbiome. Tryptophan (Trp) metabolites are the second-most widely studied metabolites in host–microbiota interactions. Intestinal microorganisms can directly transform Trp into several molecules, such as indoleacetic acid (IAA) and indolepropionic acid (IPA) (Alexeev et al., 2018), which are known to affect intestinal permeability and host immunity. BA metabolites are the third-most widely studied metabolites in host–microbiota interactions, and are the main focus of this review.

The composition of BAs is regulated by intestinal bacterial metabolism and is intrinsically linked to host physiology (Nie et al., 2015). Cell and metabolic activities are regulated by the interaction of signal molecules in the host with BA receptors (Li and Chiang, 2014; Vítek and Haluzík, 2016). These receptors include ligand-activated nuclear receptors, such as farnesoid X receptor (FXR), vitamin D receptor (VDR), and G protein-coupled BA receptor (TGR5), located on the cell surface (Li and Chiang, 2014). However, most previous studies have focused on the interaction between microorganisms and BAs, and few have specifically focused on microbial and BA receptor signaling pathways. BA receptor signaling pathways involve a number of signaling factors which provide new insights into the impact of disease and its treatment.

Therefore, in this paper we review the effects of microbes on BA synthesis and metabolism, based on recent studies. The focus is on microbiota and how the FXR, TGR5, and VDR signaling pathways affect the occurrence and development of inflammatory diseases by regulating different metabolic pathways. This will lay a foundation for understanding the regulation and treatment of various diseases.

2 Gut microbiota–BA metabolic interactions

2.1 Influence of BAs on gut microbiota

BA synthesis occurs exclusively in hepatocytes and is the only quantitatively significant cholesterol catabolic mechanism. Cholesterol 7α-hydroxylase (CYP7A1) can catalyze the conversion of cholesterol to 7α-hydroxycholesterol, which is the first step in the synthesis of BAs (Li and Chiang, 2014). Then, through continuous dehydrogenation and dehydroxylation, 7α-hydroxy-4-cholesterol-3-one (C4) is obtained, which is the common precursor of cholic acid (CA) and chenodeoxycholic acid (CDCA). Sterol 12α-hydroxylase (CYP8B1) catalyzes the hydroxylation of C4 at the C12 position, followed by cleavage of the sterol side chains of sterol 27-hydroxylase (CYP27A1) to generate CA (Fig. 1). If CYP8B1 is not metabolized, C4 will eventually be converted into CDCA (Bustos et al., 2018).

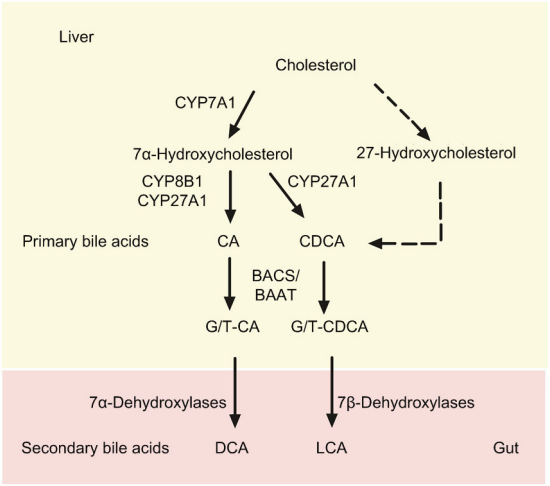

Fig. 1 Bile acid synthesis, circulation, and biological signaling activity

Primary and secondary bile acids are synthesized in the liver and intestine, respectively. CYP7A1, CYP8B1, and CYP27A1 are enzymes involved in the synthesis of primary bile acids. CYP7A1, cholesterol 7α-hydroxylase; CYP8B1, sterol 12α-hydroxylase; CYP27A1, sterol 27-hydroxylase; CA, cholic acid; CDCA, chenodeoxycholic acid; G/T-: glycine-/taurine-; DCA, deoxycholic acid; LCA, lithocholic acid; BACS, bile acid coenzyme A synthetase; BAAT, bile acid amino acid transferase

The primary BAs, CA and CDCA, are subsequently conjugated with the amino acids taurine or glycine in the liver, which increase their solubility and decrease cell membrane damage (Russell, 2003). Ninety-five percent of BAs are reabsorbed throughout the intestine and returned to the liver through the intestinal–hepatic cycle, whereas the remaining 5% are excreted via feces (Alnouti, 2009). Primary BAs that flow into the intestinal cavity can help the digestion and absorption of lipids (Begley et al., 2005). Unabsorbed primary BAs in the intestine are converted into secondary BAs by bacterial enzymes (Ridlon et al., 2006).

Secondary BAs can cause disease by regulating gut microbiota. Kakiyama et al. (2013) used 16S ribosomal gene quantification to reveal bacterial dysbiosis (such as significantly decreased *Blautia* and *Ruminococcaceae*) in cirrhotic patients compared with non-cirrhotic patients. The main reason for this was a decrease in the content of intestinal BAs. In drinking alcoholic cirrhotic patients, increased secondary BAs in feces were associated with significantly increased *Veillonellaceae* and significantly decreased *Bacteroidaceae* and *Porphyromonadaceae* in the gut microbiome (Kakiyama et al., 2014).

Liu et al. (2017) showed that the main secondary Bas, deoxycholic acid (DCA) and lithocholic acid (LCA), increased significantly after injection of organochlorine pesticides into mice, which led to an increased relative abundance of *Lactobacillus* and *Bifidobacterium* at the genus level, and may lead to human-related diseases. In the colon, almost all BAs were converted to secondary BAs (DCA and LCA) by 7α-dehydrogenation and reabsorbed via portal circulation or excreted in feces (Hofmann, 1999; Ridlon et al., 2006). Islam et al. (2011) used 16S ribosomal RNA gene cloning library sequencing and fluorescence in situ hybridization technology to characterize the composition of cecal microbiota in different dietary groups. They demonstrated that rats fed 1.25 or 5.00 mmol/kg CA developed changes in gut microbiota, especially an increased relative abundance of *Firmicute* and *Bacteroidetes*. In a mice model, FXRα could be activated by the agonist GW4064 to block the growth of aerobic and anaerobic bacteria in the ileum and cecum. This was due to the indirect involvement of BAs in the antibacterial action mediated by FXRα, which can up-regulate the mucosal defense genes in the mouse ileum (Inagaki et al., 2006). The antibacterial action of BAs is mainly via destruction of the bacterial cell membrane, and free BAs have greater destructive power.

2.2 Influence of gut microbiota on BAs

The structure of gut microbiota is influenced by BA metabolism, and gut microbiota can regulate BA synthesis. Gut microbiota can promote the secretion of small intestinal enzymes, thus affecting the synthesis of BAs (Mullish et al., 2018). Although there are many bacteria in the gut, bile salt hydrolase (BSH) is present mainly in *Clostridium* and *Lactobacillus* (Begley et al., 2005). *Lactobacillus* has the highest cholesterol removal ability and good BSH activity (Shehata et al., 2016). Therefore, colonization by intestinal bacteria is facilitated mainly by the detoxification of BAs (Ridlon et al., 2006).

However, a lack of bacterial BSH and 7-dehydroxylation activity also affects BA metabolism, due mainly to deficiencies in deconjugation of conjugated BAs and in secondary BA formation (Vrieze et al., 2014). In the intestine, glycine- or taurine-bound CA (G/T-CA) and CDCA (G/T-CDCA) are broken down by gut microbiota and 7α-dehydroxylated by anaerobic microbiota to the secondary BAs DCA and LCA (Masubuchi et al., 2016). Yamada et al. (2018) showed that mice fed a high-fat diet had higher levels of secondary BAs. This could be due to increased numbers of *Bacteroides* and *Clostridium*, and decreased *Streptococcus* and *Bifidobacterium* in the gut. *Bacteroides* can promote the deconjugation of BAs to form free BAs, while *Clostridium* promotes 7α-dehydroxylation of free BAs in the intestinal tract of mice.

The deconjugation of BAs is accomplished by many anaerobic bacteria in the intestine, while 7α-dehydroxylation of BAs is accomplished by a limited number of anaerobic bacteria. Therefore, *Bacteroides* and *Clostridium* can metabolize primary BAs and convert them into secondary BAs. However, the deconjugation and 7α-dehydroxylation of BAs can increase their hydrophobicity, leading to BA toxicity and metabolic side effects. Swann et al. (2011) analyzed the primary and second BA profiles of germ-free (GF) animals and showed that, of the primary BAs, taurocholic acid (TCA) was the most prevalent. Increased TCA levels can cause colitis

in mice that lack the interleukin-10 (*IL-10*) gene (Devkota et al., 2012). The possible reason for this is decreased BSH activity, which decreases the degradation of TCA before its conversion into secondary BAs. This indicates that the expansion of the BA pool is associated with TCA under sterile conditions. For example, compared to GF mice, traditional feeding (CONV-R) mice had lower levels of tauro-α-muricholic acid (T-α-MCA) and tauro-β-muricholic acid (T-β-MCA) in the distal small intestine, in which T-β-MCA decreased TCA-induced expression of fibroblast growth factor 15 (FGF15) outside the ileum and in vivo (Enright et al., 2017). This indicated that the intestinal microbiota could decrease T-MCA levels and promote FGF15 expression to inhibit CYP7A1 and the synthesis of BAs (Li-Hawkins et al., 2002; Sayin et al., 2013). However, high concentrations of TCA may directly affect the heart development of GF animals (Swann et al., 2011). Therefore, the imbalance of gut microbiota not only can change intestinal BAs, but also can be associated with many other diseases.

Gut microbiota play a role not only in the small intestine, but also in other parts of the intestine (Sayin et al., 2013). Gut microbiota have a profound impact on BA metabolism through the deconjugation, dehydrogenation, and dehydration of primary BAs in the small intestine and colon. For example, gut microbiota affect mainly FXR target genes in the ileum. FXR-dependent activation of FGF19 in the ileum regulates BA synthesis in the liver, but the binding of FGF19 with fibroblast growth factor receptor 4 (FGFR4) can inhibit BA synthesis (Inagaki et al., 2005; Zimmer et al., 2012). However, the synthesis of BAs is also regulated by peroxisome proliferator-activated receptor α (PPARα) ligands. PPARα ligands can regulate BA distribution by increasing CA and decreasing CDCA (Hunt et al., 2000). Dehydroxylation of CDCA results in CA, which is toxic to hepatocytes and has been associated with the development of colon cancer (Hofmann, 2004). In addition, CA and CDCA derived from primary BAs can be converted into the secondary BAs DCA and LCA, respectively, by *Acetatifactor* and *Bacteroides* 7α- and 7β-dehydroxylases (Pathak et al., 2018). Therefore, gut microbiota are the main factors regulating BA metabolism (Joyce et al., 2014).

3 BA-related molecules, microbiota, and diseases

BAs are the product of lipid metabolism in the liver and intestine. They are potent ligands for nuclear receptors including FXR, pregnane X receptor (PXR), and VDR, and are endogenous agonists for the TGR5. These receptors play an important role in the synthesis, regulation, and metabolism of BAs (Degirolamo et al., 2011; Kundu et al., 2015). In recent years, the role of gut microbiota in causing or alleviating diseases had attracted much attention. Therefore, clarifying the interaction between BAs and gut microbiota will enable a better understanding of the causes of these diseases and could lead to new treatment options. This part of the review summarizes the roles of the FXR, TGR5, and VDR signaling pathways in different diseases.

3.1 Relevance of FXR for diseases

The most important step in the regulation of BA metabolism by FXR is the inhibition of bile acidosis by inhibition of CYP7A1, including via two feedback regulation pathways. In one pathway, FXR promotes the synthesis of BAs through the action of the bile salt export pump (BSEP) in the liver, thus inducing the expression of small heterodimer partner (SHP). Then, the SHP protein inactivates liver receptor homolog-1 (LRH-1), a signaling molecule required for expression of CYP7A1 (Lu et al., 2000), thus inhibiting expression of CYP7A1. In the other pathway, BA-dependent FXR activation induces FGF15/19 binding to FGFR4, thereby inhibiting CYP7A1 (Fig. 2) (Cariello et al., 2017).

3.1.1 Metabolic syndrome

The FXR is significant in the regulation of gut microbiota. It regulates BA homeostasis and BA enterohepatic circulation, and affects a variety of metabolic diseases (Matsubara et al., 2013; Peng et al., 2016; Jin et al., 2019). BAs and the FXR axis have been shown to regulate fat and glucose metabolism. FXR activation improves insulin sensitivity, steatosis, and obesity induced by a high-fat diet (Cariou et al., 2006; Zhang et al., 2006; Ma et al., 2013). The insulin sensitivity of metabolic syndrome patients is improved by transplanting fecal microbes from glucose-sensitive humans (Vrieze et al., 2012), possibly

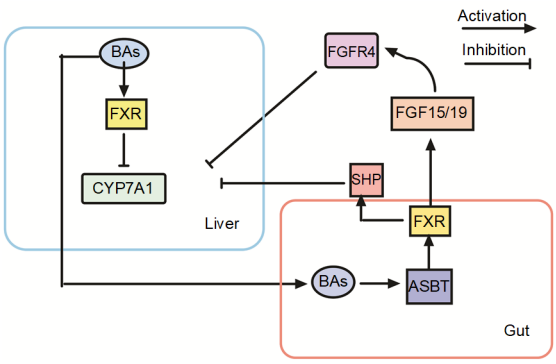

Fig. 2 Interaction between BAs and the FXR signaling pathway

FXR regulates BA metabolism through three feedback pathways, two of which inhibit bile acidosis by inhibiting CYP7A1. FXR can also regulate intestinal mucosal immune responses by the gut microbiome. BAs, bile acids; FXR, farnesoid X receptor; CYP7A1, cholesterol 7α-hydroxylase; SHP, small heterodimeric partner; FGFR4, fibroblast growth factor receptor 4; FGF15/19, fibroblast growth factor 15/19; ASBT, apical sodium-dependent bile acid transporter

because changes to gut microbiota affect the physiological response of the host by regulating the FXR signal pathway. The main mechanism is CDCA inhibition of hepatocyte nuclear receptor expression through the FXR pathway, thereby decreasing transcription of phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphate dehydrogenase deficiency (G6PD) (Yamagata et al., 2004). Therefore, FXR knockout mice have accelerated glycolysis and lipogenic gene transcription, while intestinal absorption of glucose is delayed (Duran-Sandoval et al., 2005).

In addition, gut microbiota can induce the up-regulation of BA synthase CYP7A1. Mice treated with antibiotics can have decreased gut flora diversity and abundance, which is related to the synthesis of BAs (Reijnders et al., 2016). A decrease in *Lactobacillus* leads to a decrease in BSH, thereby increasing T-β-MCA levels (Jiang et al., 2015). However, increasing T-β-MCA inhibits intestinal FXR signaling and decreases FGF15 levels, thereby increasing CYP7A1 transcription and BA synthesis in the liver (Xie et al., 2017). Endogenous BA T-β-MCA inhibits the FXR signaling pathway, leading to decreases in high-fat diet-induced obesity, insulin resistance, and nonalcoholic fatty liver disease, which suggests that FXR may be a potential drug target for metabolic syndrome (Gonzalez et al., 2016).

3.1.2 Liver diseases

Gastrointestinal bleeding and the lack of BAs and stomach acid in patients with cirrhosis can lead to increased aerobic bacteria in the intestine and movement of colonic bacteria into the jejunum and duodenum, causing excessive growth of intestinal bacteria. For example, an increase in bacteria such as *Enterobacteriaceae* produces more lipopolysaccharide (LPS), which increases the incidence of inflammation. However, high concentrations of bile salts can decrease the growth of intestinal bacteria, mainly because bile salts can activate FXR and induce the expression of antimicrobial peptides (Begley et al., 2005; Inagaki et al., 2006; Ridlon et al., 2006). Ananthanarayanan et al. (2001) reported that the BSEP promoter contains an FXR response element, and FXR can be directly bound to the BSEP promoter. LCA is an inducer of liver damage, and the expression of BSEP is decreased by FXR antagonism, thereby leading to a decrease in BA secretion, increasing liver BA concentration, and causing liver damage.

On the other hand, deconjugation of BSHs in gut bacteria can generate primary BAs. These are converted into secondary BAs by 7α-dehydroxylase bacteria. As these bacteria change in cirrhotic patients, the bioconversion of primary BAs into secondary BAs is decreased. BAs produced in the gut lumen can bind to FXR to produce FGF19 and enter the portal vein circulation to bind to FGFR4 (Woodhouse et al., 2018). The result is inhibition of CYP7A1 enzyme activity. This affects the synthesis of primary BAs and, in turn, destroys the structure of microbiota.

In addition, FGF19 is a hormone-like factor secreted by the ileum. It can inhibit the secretion of BAs, so when FGF19 is deficient it causes idiopathic BA malabsorption (BAM). This is a result mainly of impaired processing, release or breakdown of FGF19, or improper response of the FGF19 receptor FGFR4 in hepatocytes (Vijayvargiya et al., 2017). Therefore, decreased conjugated BA secretion leads to a decreased BA concentration in the gut lumen, which weakens the inhibition of bacterial growth. This vicious cycle causes cirrhosis of the liver. Out et al. (2015) reported that *Bifidobacterium* and *Lactobacillus* could decrease the BA content of intestinal epithelial cells by inhibiting the absorption of BA molecules, and ultimately down-regulate the FXR/FGF15 pathway, enhance CYP7A1 activity and

promote BA synthesis in the liver. Degirolamo et al. (2014) reported that administration of the probiotic cocktail formulation VSL#3 could change the abundance of microbial flora in mice feces, leading to increased counts of *Firmicutes* and *Actinobacteria*, while decreasing *Bacteroidetes* and *Proteobacteria*. Alterations in intestinal microbiota cause down-regulation of ileal FGF15, leading to increased expression of *Cyp7a1* and *Cyp8b1* genes (Degirolamo et al., 2014). Therefore, these studies show that gut microbiota disorders can affect liver function through changes in BA metabolism.

3.1.3 Inflammatory diseases

FXR can also regulate intestinal mucosal immune responses by gut microbiota. The FXR, nuclear factor κB (NF-κB), and Wnt/β-catenin signaling pathways are closely related. In recent years, many studies have reported the relationship between FXR and inflammatory response. Gadaleta et al. (2011) reported the direct involvement of NF-κB in the repression of FXR activity by overexpression of NF-κB subunits p50 and p65. The decreased FXR activity resulted in less inhibition of intestinal inflammation, leading to the development of chronic intestinal inflammation. However, LPSs produced by gut microbiota can stimulate NF-κB to aggregate inflammatory cells and increase the level of inflammatory factors (Carr and Reid, 2015). FXR can also inhibit NF-κB and thus decrease liver inflammation (Carr and Reid, 2015). Studies have reported that *Clostridium* affects BA metabolism in the intestine and inhibits FXR activation (Theriot et al., 2016). FXR deficiency leads to the early death of mice, and promotes Wnt signaling through the production of neutrophils, macrophages, and tumor necrosis factor-α (TNF-α), thereby causing gut inflammatory diseases (Modica et al., 2008). Wolfe et al. (2011) reported that increased hepatic BAs play a critical role in hepatic tumorigenesis in FXR knockout mice. The increased BAs may stimulate temporal activation of the Wnt/β-catenin pathway independently of FXR and promote the development of hepatocellular carcinoma (HCC) in FXR knockout mice. Activation of FXR by agonist ligands can also inhibit the expression of inflammatory mediators in NF-κB activation in both HepG2 cells and primary hepatocytes cultured in vitro (Wang et al., 2008). However, the exact mechanisms by which BAs induce β-catenin and NF-κB are currently unclear. Further exploration of the role of the gut microbiota-mediated FXR signaling pathway in related inflammatory diseases could assist in the development of new therapeutic strategies.

3.2 Relevance of TGR5 for diseases

Gut flora activate TGR5 expression by affecting intestinal endocrine cells, thereby affecting the metabolism of glucose and energy, and have anti-inflammatory and immunomodulatory effects (Katsuma et al., 2005; Watanabe et al., 2006). TGR5 has at least three important functions: (1) BAs can induce glucagon-like peptide-1 (GLP-1) production in the enteroendocrine cell line STC-1 via TGR5 activation, leading to increased insulin secretion and decreased glucose, thereby affecting glucose metabolism; (2) binding of BAs to TGR5 increases intracellular cyclic adenosine monophosphate (cAMP) and results in the transcription of the type 2 iodothyronine deiodinase (*Dio2*) gene encoding type 2 deiodinase (D2) which converts thyroid hormone (T4) into the more active triiodothyronine (T3), thereby increasing basic metabolism and energy consumption; (3) BAs can increase the concentration of cAMP and inhibit the production of pro-inflammatory factors such as TNF-α, IL-1, and IL-6 induced by LPS through TGR5. BAs can also decrease the transcriptional activity of NF-κB, thereby inhibiting the expression of pro-inflammatory cytokines (Fig. 3). Recent studies have found that TGR5 cellular signaling can regulate the occurrence of metabolic syndrome and inflammatory diseases. Here, we review research progress relating to the role of TGR5 in metabolic syndrome and related inflammatory diseases.

3.2.1 Metabolic syndrome

Changes to the gut microbiome can improve insulin resistance, control blood sugar, and treat metabolic syndrome through BA secretion, regulation of GLP-1, and decreasing chronic inflammatory reaction (Sinclair et al., 2018). The gut microbiome regulates TGR5 signal transduction by producing agonists, which can promote the secretion of GLP-1, leading to the release of glucose-dependent insulin. GLP-1 plays a vital role in post-meal insulin secretion and appetite suppression (Baggio and Drucker, 2007). The main reason is that *Acetatifactor* and *Bacteroides*

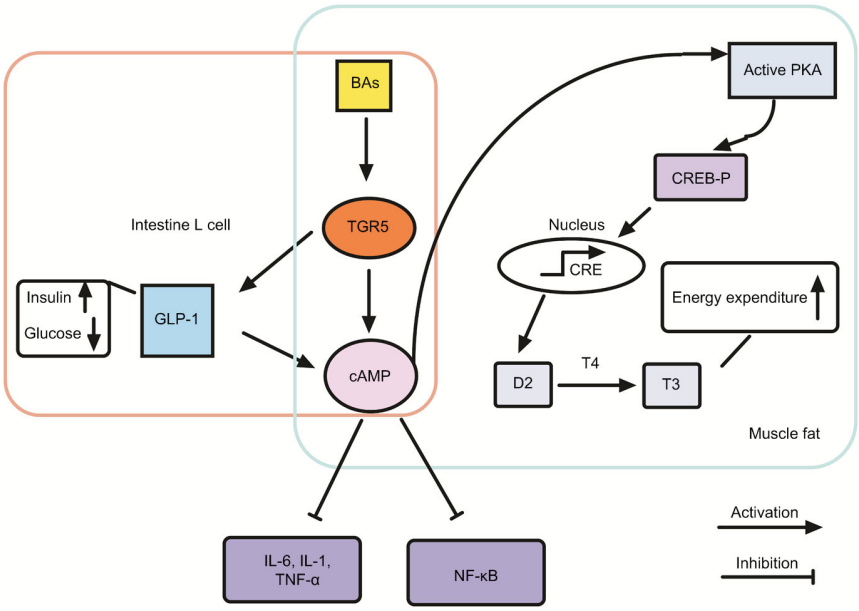

Fig. 3 Interaction between BAs and the TGR5 signaling pathway

These are three major metabolic pathways in the TGR5 signaling pathway. BAs can affect glucose and energy metabolism by activating TGR5, and are involved in anti-inflammatory immune regulation. BAs, bile acids; TGR5, G protein-coupled BA receptor; cAMP, cyclic adenosine monophosphate; GLP-1, glucagon-like peptide-1; D2, type 2 deiodinase; T4, thyroid hormone; T3, triiodothyronine; PKA, protein kinase A; CRE, cyclic AMP response element; CREB-P, cyclic AMP response element binding protein

in intestinal bacteria have high BSH, 7α-dehydroxylase, and 7β-dehydroxylase activity and can produce LCA from CDCA and UDCA. LCA can activate TGR5 signaling and stimulate GLP-1 secretion by L cells, thus promoting fat browning and improving insulin signaling and glucose metabolism (Pathak et al., 2018). Laverdure et al. (2018) showed that a high-fat diet significantly increased GLP-1 secretion and fecal methanogen content, and that the use of antibiotics to destroy methanogens could decrease insulin secretion. This suggests that changes in methanogen concentration may play an important role in the secretion of GLP-1 in obese patients. Methane increases intracellular cAMP content by stimulating GLP-1 secretion.

Further studies have found that the TGR5 can also increase the level of cAMP, which can induce the production of GLP-1 in intestinal endocrine cells, promote the dephosphorylation of glycogen synthase in hepatocytes, and promote glycogen synthesis. Thus, it has a significant effect on decreasing blood sugar (Lee et al., 2007). Vrieze et al. (2014) reported that oral vancomycin could significantly decrease the diversity of gut microbiota and the content of secondary BAs in feces, and decrease peripheral insulin sensitivity. Watanabe et al. (2006) found that BAs bind to TGR5 in brown adipose tissue and skeletal muscle, and increase intracellular cAMP. This can increase D2 enzyme activity, which converts T4 to T3 and increases energy expenditure as heat, thus significantly decreasing the weight of mice fed high-fat diets. Therefore, the BA-TGR5-cAMP-D2 signaling pathway plays an important role in regulating energy homeostasis. However, the effect of gut microbiota on this energy metabolism-signaling pathway has not been reported.

3.2.2 Inflammatory diseases

Cholesterol is fermented by microorganisms in vivo to produce BAs, which are metabolized by microorganisms in the distal small intestine and colon to produce secondary BAs (Sonnenburg and Bäckhed, 2016). Taurine- and glycine-bound BAs can promote inflammation and anti-inflammation, respectively, by activating membrane receptor TGR5 on cell surfaces, while an excessive BSH-containing gut microbiome can change TGR5-mediated inflammatory and anti-inflammatory activity by dissociating the bound BAs. TGR5 is expressed mainly in monocytes and macrophages. Mononuclear phagocytes can secrete a variety of inflammatory mediators and play an

important role in regulating inflammatory response. Therefore, gut microbiota help regulate BA composition and related signaling, which is important for the development and prevention of disease.

Keitel et al. (2008) found that, after activation of TGR5 in liver Kupfer cells by BAs or TGR5 agonists, intracellular cAMP levels were elevated. This inhibited LPS-induced up-regulation of TNF-α, IL-6, IL-1β, and IL-1α. The synthesis of LPS-stimulated pro-inflammatory cytokines was significantly higher in $TGR5^{-/-}$-isolated macrophages than in $TGR5^{+/+}$ mice (Pols et al., 2011). This further supports the role of TGR5 signaling in the down-regulation of the inflammatory response to Gram-negative bacteria. In addition, the anti-inflammatory effect of TGR5 is mediated mainly by the inhibition of pro-inflammatory transcription factor B (e.g. NF-κB) (Pols et al., 2011). For mice without the *TGR5* gene, the mRNA expression levels of various pro-inflammatory genes targeted by NF-κB were higher than those of macrophages from wide-type (WT) mice (Wang et al., 2011). Therefore, a metabolic balance between BAs and the microbiome is essential to prevent disease.

Although many studies have shown that activating TGR5 can improve metabolism and immunity, there is still much controversy about its function and mechanism. Further research into the TGR5 signaling pathway will provide a more complete understanding of the physiological and pathological roles of TGR5.

3.3 Relevance of VDR for diseases

The VDR-encoded nuclear transcription factor forms dimers with the retinoid X receptor (RXR). The dimers exert a series of physiological effects through endogenous or exogenous ligands. Bacterial metabolites also have a function through the VDR–RXR dimer. VDR is closely related to bacteria. *VDR* gene expression in GF and conventionally raised mice is different, indicating that this gene plays an important role in the balance of intestinal microbes (Wang et al., 2016).

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation associated with intestinal microecological disorders and autoimmune disorders. Decreased expression of VDR leads to the development of ulcerative colitis, dysplasia, and colitis-associated colorectal cancer (Wada et al., 2009). VDR is expressed in hepatocytes, and VDR ligands can inhibit the synthesis of BAs. It plays an important role in maintaining bile homeostasis by inhibiting the transcription of the *CYP7A1* gene in the liver and inducing the detoxification mechanism of LCA in the intestine (Cheng et al., 2014). In addition, vitamin D deficiency and decreased VDR are also related to obesity and diabetes. When bacteria invade the intestine, they induce VDR dysfunction. Under the action of antigen, intestinal mucosal tissue T cells are activated, Th17 cells proliferate and differentiate, and the inflammation is regulated by the release of inflammatory cytokines such as IL-17, IL-6, and IL-8 (Espinosa et al., 2009). At the same time, Th17 cytokines can also induce the expression of chemokines such as monocyte chemoattractant protein-1 (MCP-1), and mediate local infiltration of inflammatory cells, leading to intestinal mucosal tissue damage (Espinosa et al., 2009). Jin et al. (2015) found that VDR affected intestinal microflora and correlated the VDR-associated bacterial changes with clinical diseases. Decreased VDR expression in the intestine can lead to microorganism imbalance, which leads to decreased concentrations of butyrate-producing bacteria, resulting in susceptibility of VDR knockout mice to chemical-induced colitis (Sun, 2016).

Many studies have shown that changes in gut microorganisms play a key role in the occurrence and development of colorectal cancer (Yang et al., 2013; Vogtmann and Goedert, 2016). VDR-mediated LCA detoxification may help vitamin D in the prevention of colon cancer. The mechanism of VDR in colorectal cancer may be related to gut microbial interactions and inflammatory responses (Sun, 2017). Wu et al. (2010) found that VDR inhibited the NF-κB signaling pathway and decreased the number of harmful bacteria, resulting mouse mortality caused by *Salmonella* infection.

Further research into the role of VDR in microbial infection-related diseases will help elucidate the function and mechanism of VDR in immune regulation. Understanding the interaction between VDR and gut microbiota could enable new targets for the prevention and treatment of various diseases.

4 Conclusions

The gut microbiota interact with BAs to affect the hydrophobicity, toxicity, and regulation of BAs through biotransformation reactions. BA pools have a

central role in physiology and physiopathology. Disorders of BA pools caused by diseases or temporary use of antibiotics may lead to many diseases. The FXR, TGR5, and VDR signaling pathways are influenced by gut microbiota during BA synthesis and metabolism. Therefore, there has been an increasing research focus on the microbial community structure, especially in unhealthy organisms, to determine how microorganisms can interfere with these pathways. Studying microbial–BA–host interactions to develop BA signaling as an intervention target for the treatment of cholestasis diseases and tumor-related diseases will be a significant advancement in the development of personalized therapeutic and diagnostic tools using microorganisms.

Contributors

Er-teng JIA and Qin-yu GE designed the research. Er-teng JIA wrote the manuscript. Zhi-yu LIU, Min PAN, Jia-feng LU, and Qin-yu GE provided guidance on the writing of this review. All authors read and approved the final manuscript.

Compliance with ethics guidelines

Er-teng JIA, Zhi-yu LIU, Min PAN, Jia-feng LU, and Qin-yu GE declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：肠道微生物调节疾病中胆汁酸代谢相关的信号通路

概　要：近十年来，微生物与胆汁酸代谢的相互作用越来越受到关注。胆汁酸不仅参与营养物质的代谢，而且在调节宿主生理活动的信号转导中也起着重要作用。已有研究表明，微生物调控的胆汁酸代谢对许多疾病都有显著的影响，但对微生物受体信号通路调控疾病的相关研究并不多。本文综述了近年来有关法尼醇受体（FXR）、G 蛋白偶联胆汁酸受体（TGR5）和维生素 D 受体（VDR）信号通路在健康和疾病的微生物-宿主相互作用中的核心作用。研究这些信号通路之间的关系，有助于我们了解人类疾病的发病机制，为人类疾病的治疗提供新的解决方案。

关键词：肠道微生物群；胆汁酸；法尼醇受体；维生素 D 受体；代谢